Can the Movement of the Air Bubbles After Embryo Transfer Predict the Success of IVF Treatment?

Embryo Transferi Sonrası Hava Kabarcıklarının Hareketi IVF Başarısının Göstergesi Olabilir Mi?

A Randomized Clinical Trial

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Özet

Amaç: Trabsabdominal ultrason eşliğinde yapılan IVF sikluslarında hava kabarcıklarının transfer sonrasındaki hareketinin gebelik oranları üzerine olan etkisinin değerlendirilmesi. Gereç ve Yöntem: Çalışmaya dahil edilen ultrason eşliğinde yapılan 136 taze, fundal embriyo transferi sonrasındaki hava kabarcıklarının hareketine göre 3 gruba ayrıldı. Grup 1 (n-101), ejeksiyon ile hava kabarcıkları uterin fundusa doğru ilerleyenler; Grup 2 (n=30), ejeksiyon ile hava kabarcıkları servikal kanala doğru ilerleyenler; ve Grup 3 (n=30), trasnfer sonrası hava kabarcıklarında hiçbir hareket izlenmeyenler. Temel sonuç, klinik gebelik oranıdır. Bulgular: Bütün transferlerin 53 (%38,9) tanesi klinik gebelik ile sonuçlanmıştır. Bu klinik gebeliklerin %75' i grup 1' de; %1,9' u grup 2' de; %22,6' sı da grup 3' te idi. Klinik gebelik oranları grup1, 2 ve 3' te sırasıyla %39,6, %20, %40 olarak bulundu. Trasnfer sonrası hava kabarcıklarının servikal kanala ilerlediği grupta gebelik oranlarında önemsenecek bir düşüş izlenmiş olsa da bu oran istatistiksel anlamlılığa ulaşmamıştır (p=0,67). Tartışma: Transfer sonrası hava kabarcıklarının servikal kanala doğru hareket etmesi gebelik oranlarının düşübeliceği konusunda kötü bir prognostik faktör olabililir ve IVF tedavisinde başarıyı etkileyebilir

Anahtar Kelimeler

Embryo Transferi; Hava Kabarcığı; İn Vitro Fertilizasyon

Abstract

Aim: We aim to evaluate the effect of the movement of air bubbles after embryo transfer (ET) on pregnancy outcomes under transabdominal ultrasound-guided ET in IVF cycles. Material and Method: One hundred and thirty six (136) ultrasound-guided fresh fundal ETs included in this study were divided into 3 groups according to the movement of air bubbles after ET. Group 1 (n=101) consisted of ETs in which the air bubbles moved towards the uterine fundus with ejection immediately after transfer; Group 2 (n=5) consisted of ETs in which the air bubbles moved towards the cervical canal after transfer; Group 3 (n=30) consisted of ETs in which no movement of air bubbles was observed after transfer. The primary outcome was the clinical pregnancy rate. Results: Of all the transfers, 53 (38.9%) resulted in a clinical pregnancy. Of these clinical pregnancies, 75% was in group 1, 1.9% was in group 2 and 22.6% was in group 3. The clinical pregnancy rates were 39.6%, 20%, and 40% in groups1, 2, and 3 respectively. The clinical pregnancy rates were dramatically reduced in cases with the air bubbles moving towards the cervical canal after transfer, although this did not reach statistical significance (p=0.67). Discussion: The movement of air bubbles towards the cervical canal after transfer can reflect a poor prognostic outcome in terms of lower pregnancy rates and can influence the success of IVF treatment.

Keywords

Embryo Transfer; Air Bubble; In Vitro Fertilization

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Introduction

The woman's age, ovarian reserve, embryo quality, endometrial receptivity, and ET technique can be considered factors determining the success of IVF treatment and predicting pregnancy outcome [1-3]. Despite technological developments and the current standardizations providing improvements in some of these factors, major advances related to the ET technique have not been recorded. After an understanding of the importance of this step, most studies have recently focused on providing standardization and improvement of ET technique that is the final and crucial step of successful IVF.

Many factors determine the outcomes of ET technique: the catheter tip placement and withdrawal of the catheter, the catheter loading technique, the ejection speed, ET depth, the location of air bubbles, and the physician's experience [4]. A targeted successful ET prevents endometrial injury and the induction of uterine contractions; it protects embryos and places embryos in an optimal position within the uterine cavity, thus maximizing embryo implantation. Ultrasound (US)-guided ET can overcome adverse effects including endometrial injury and the induction of uterine contractions during ET and it can determine ET depth and the location of air bubbles [5-8].

The air bubbles loaded into the ET catheter with the embryo(s) could be considered as an identifier for determining the final position of the embryo(s) in the uterine cavity during US-guided ET. Studies that have evaluated optimal ET depth within the uterine cavity reported that fundal embryo transfer is associated with the highest pregnancy rates (PRs) but this lacks a consensus [9-11]. However, movement of air bubbles after ET may affect IVF success and pregnancy outcomes. Due to the lack of sufficient research evaluating the relationship between the movement of the air bubbles and pregnancy outcomes, we aim to evaluate the effect of the movement of air bubbles after ET on pregnancy outcomes under transabdominal US-guided ET in IVF cycles .

Material and Method

Participants

This retrospective study was based on the analysis of the medical records of patients that underwent US-guided fresh ETs performed by a single physician (C.F.) at Yeditepe University Hospital IVF center, Istanbul, Turkey. One hundred and thirty six (136) US-guided fresh fundal ETs included this study were divided into 3 groups according to the movement of air bubbles after ET. Group 1included 101 ETs in which the air bubbles moved towards the uterine fundus with ejection immediately after transfer; Group 2 consisted of 5 ETs in which the air bubbles moved towards the cervical canal after transfer; Group 3 consisted of 30 ETs in which no movement of the air bubbles was observed after transfer. The inclusion criteria stated participants had to be primary infertile patients undergoing IVF treatment due to tubal factors, male factors, or unexplained infertility, with FSH (follicle-stimulating hormone) levels on cycle day 3 of ≤12 mIU/mL, BMI ≤25 kg/m2, and between 18 to 40 years-old. Patients with blood present on the catheter during the transfer procedure, with a difficult transfer, or with the use of a firmer catheter were excluded from the study. Data collected included age, etiology, and duration of infertility, FSH levels on cycle day 3, total dosage of gonadotropins, duration of stimulation, total number of oocytes retrieved, the number of embryos transferred, the movement of air bubbles after ET, and clinical PR.

Assisted reproduction procedures

All patients underwent controlled ovarian stimulation with antagonist (Cetrotide; Serono, Geneva, Switzerland) protocol and stimulation with recombinant FSH (Gonal F; Serono, Geneva, Switzerland). Initial gonadotropin doses (150 to 450 IU/daily) were based on age, serum FSH and E2 (estradiol) levels on cycle day 3, and antral follicle count. Ovarian response was monitored via serial sonographic measurements and serum E2 levels and doses were adjusted according to ovarian response. Recombinant hCG (human chorionic gonadotropin) (Ovitrelle, 250 mg; Serono) was administered when at least two follicles reached a mean diameter of >17 mm. Oocyte retrieval was performed 36 h after the injection of hCG. Standard ICSI techniques were carried out for the fertilization of the oocytes. According to maternal age, indication for IVF, and the number and quality of embryos available, one or two embryos were transferred on day 3 or 5. On the day of retrieval, vaginal crinone gel (Crinone 8%, 90 mg; Merck Serono, Central Pharma Ltd., Bedfordshire, UK) daily was started for luteal phase support. Serum beta-hCG levels were performed 12 days after ET. A clinical pregnancy was defined as the presence of a fetal sac visualized by a transvaginal US.

Embryo selection and embryo transfer

The best quality embryos to be transferred were determined according to morphology and cleavage criteria. All ETs were performed by one operator (C.F.) under transabdominal US guidance performed by one physician (P.O.). Loading the catheter and the ET procedure were performed as described in our previous study (11). The movement of air bubbles after ET was noted by the operator for future analysis.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 21 (SPSS, Chicago, IL). Values are expressed as mean± SD or number and percentage. P <0.05 was considered significant. The chi-square test or Fisher's exact test was used to compare categorical variables. Normal distributions of continuous variables were assessed by t test. Non-normally distributed metric variables were tested via the Kruskall Wallis test and the Mann-Whitney U test. A multivariable logistic regression model was used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) for the likelihood of clinical pregnancy and air bubble movement after transfer in the three groups.

Results

Fax: +902165784948, Of all the groups, the patient demographics including mean age (years), mean duration of infertility (years), and etiology of infertility are presented in Table 1. There was no significant difference among the three groups with respect to these parameters. The comparison of outcomes related to COH including FSH levels on cycle day 3, total dosage of go-

Table 1. The patient demographics

Variables	Group 1 (n=101)	Group 2 (n=5)	Group 3 (n=30)	P value
Age (years)	34,02±5,48	33,4±6,54	32,9±5,66	0,68
Duration of infertility (years)	5,76±4,31	4,0±1,73	4,36±4,02	0,15
Etiology of infertility				
Tubal factor	24 (23,7%)	1 (20%)	10 (33,3%)	
Male factor	42 (41,5%)	3 (60%)	12 (40%)	0,73
Unexplained infertility	35 (34,6%)	1 (20%)	8 (26,6%)	

All values are expressed as mean ± SD or number. * p < 0.05, significant difference.

nadotropins, duration of stimulation, total number of oocytes retrieved, and the number of embryos transferred are shown in Table 2. There was no significant difference with regard to the distributions among the three groups. Of all the transfers, 53 (38.9%) resulted in a clinical pregnancy. Of these clinical pregnancies, 75% was in group 1, 1.9% was in group 2, and 22.6% was in group 3 (Table 2). The clinical PRs were 39.6%, 20%, and 40% in groups1, 2 and 3 respectively (Table 3). The clinical PRs dramatically reduced in cases with air bubbles moving towards the cervical canal after transfer, although this did not reach statistical significance (p=0.67). The clinical PR appears to be associated with air bubble movement after transfer.

Table 2. The comparison of outcomes related to COH and clinical pregnancy rates between groups

Variables	Group 1 (n=101)	Group 2 (n=5)	Group 3 (n=30)	P value
FSH levels on cycle day 3	7,71±3,55	9,80±3,34	7,63±3,18	0,35
Total dosage of gonadotropins	2894,80±1001,93	2910,00±697,67	2771,66±1069,61	0,06
Duration of stimulation	9,61±1,02	9,80±,44	9,40±1,06	0,26
Total number of oocytes retrieved	6,11±3,66	4,60±,89	7,20±3,62	0,21
Number of embryos transferred	1,40±,49	1,20±,44	1,50±,50	0,39
Clinical pregnancy rates	40 (75.5%)	1 (1,9%)	12 (22.6%)	0,67

All values are expressed as mean ± SD. * p < 0.05, significant difference.

Table 3. The relation between PR and air bubble movement after transfer

Variables	Pregnancy rates	OR	p value	95% CI
Group 1 (n=101)	39.6%	1.11	0.79	0.50-2.45
Group 2 (n=5)	20%	0.38	0.64	0.04-3.49
Group 3 (n=30)	40%	1.05	0.89	0.46-2.42

Discussion

Much fewer studies have focused on assessing the efficacy of ET technique on IVF treatment than those focusing on other variables including ovulation induction protocols, oocyte retrieval techniques, embryo quality, and uterine receptivity. Although little attention has been given to ET technique, it has recently been recognized as an important variable in the success of IVF treatment . Several studies have recently analyzed variables affecting successful ET such as US-guided ET, mock transfer, type of catheter, loading the catheter, blood or mucus effects, retained embryos, uterine contractions, and facility of the procedure. Studies which evaluated the effect of US-guided ET indicated that US-guided ET appears to improve IVF success and is significantly associated with increased PRs [5-8].

However, during US-guided ET the ultrasonographic visualization of newer ET catheters and air bubbles, an identifier of the position of the embryos, is one of the most important developments regarding ET technique. According to the outcomes of studies that focused on the potential effect of embryo replacement depth on IVF outcomes, fundal transfer is associated with the highest PRs. In a retrospective analysis of 5,055 US-guided ETs, Tıras et al. found that when air bubbles were sonographically closer to the fundus, ongoing PRs were higher [9]. Furthermore, in our previous study, we also demonstrated that clinical PRs appeared higher in cases with air bubbles closer to the fundus, and a distance of <10 mm from the fundal endometrial surface seems likely to be the optimal position of the air bubbles for successful ET. A prospective data-analysis of 367 US-guided ETs found the highest PRs in fundal transfers [12]. A retrospective cohort study designed by Friedman et al. included 315 non-donor blastocyst (BT) transfers and suggested that BT closer to the fundus is associated with a higher PR [10].

Besides air bubble localizations, air bubble movements after transfer could influence the success of the ET technique and IVF success. A retrospective analysis of 7,489 US-guided ETs revealed the movement of air bubbles towards the uterine fundus after ET was associated with higher PRs, and PRs significantly decreased with the movement of air bubbles towards the cervical canal after transfer [13]. There are insufficient studies to evaluate the impact of air bubble movement after transfer on IVF outcomes. Therefore, in the present study, we analyzed the effect of the movement of air bubbles after ET on pregnancy outcomes in 136 US-guided fresh fundal ETs. We only analyzed fundal ETs to minimize bias resulting from air bubble localizations. In the light of our results, we revealed increased clinical PRs in cases with air bubbles moving towards the uterine fundus after transfer or no movement of air bubbles, and PRs were reduced in cases with the air bubbles moving towards the cervical canal after transfer. The decreased PRs associated with the movement of air bubbles towards the cervical canal after transfer could result from the escape of the embryos back into the cervical canal or undesired uterine contractions [3]. No ectopic pregnancies were seen in the movement of air bubbles towards the uterine fundus after ET. All 136 US-guided fresh ETs were performed by one experienced physician; this seems to be advantage for improvement of ET technique and it may overcome little potential variation resulting from ET technique. In our study, the movement of air bubbles towards the cervical canal after transfer was observed in only 5 patients and significantly more air bubbles moved towards the uterine fundus. The small sample size, especially in group 2, might be a limiting factor but it is a preliminary study. The present study can contribute to an understanding of the importance of the movement of air bubbles in the success of IVF treatment.

In the our previous study, we concluded that the air bubble position, as an identifier of final embryo position at ET, could be considered as a variable to determinate PRs, although it cannot be predicted. However, our current study indicated that clinical PRs appeared higher in cases with air bubbles moving towards the uterine fundus or not moving while PRs decreased with

air bubbles moving towards the cervical canal after transfer. Therefore, given the importance of ET, the movement of air bubbles towards the cervical canal after transfer can reflect a poor prognostic outcome in terms of lower PRs and it can influence the success of IVF treatment. Further well-designed randomized controlled trials are required to evaluate the impact of the movement of air bubbles on IVF treatment in the future.

Competing interests

The authors declare that they have no competing interests.

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